REMARKS

Applicants appreciate the thorough examination of the present application as evidenced by the Office Action dated March 25, 2004 ("Office Action"). Claims 1, 3-21, 23-40, 42, 43 and 45-54 are pending in the present application upon entry of the present Amendment. Claims 2, 22, 41 and 44 have been canceled herein without prejudice. Claims 1, 3-5, 12-18, 23, 27, 32, 35, 36, 40, 42, 43, 48 and 49 have been amended herein. New claims 50-54 have been added. Support for the claim amendments and new claims can be found in the specification and claims as originally filed and as discussed further below. Applicants respectfully submit that these amendments and new claims do not present new matter, and respectfully request entry thereof. The concerns raised by the Examiner are addressed below as set forth in the Office Action.

I. Objections to the Disclosure and Claims

The specification has been amended as presented above in order to address the objections to the disclosure as presented in the Office Action on page 2. More specifically, the specification has been amended to recite "Figures 37 through 50" where relevant.

Applicants have amended the priority claim to note that the present application is a National Phase application of PCT/US01/18611 filed on June 8, 2001, published in English, which claims priority from United States patent application 09/591,642, filed June 9, 2000, and is a continuation of United States patent application 09/591,642, filed June 9, 2000, which is a continuation-in-part of U.S. patent application 09/244,340 to Toh et al., filed February 4, 1999 and U.S. patent application 09/372,954 to Toh et al., filed August 12, 1999. Applicants hereby confirm that the present application claims priority from United States patent application 09/591,642, filed June 9, 2000, **and** is a continuation of the '642 application. Applicants respectfully submit that the priority claim **does not** recite that the '642 application is a continuation of itself.

Additionally, claim 36 has been amended as suggested by the Examiner.

Accordingly, Applicants respectfully submit that the objections to the disclosure and claims have been overcome, and respectfully request that these objections be withdrawn.

II. Consideration of References Cited on Form PTO-1449

It is Applicants' understanding that although crossed out, the International Preliminary Examination Report cited on Form PTO-1449 filed January 21, 2003 and Downey et al. (no. 26) and Toh et al. (no. 60) cited on Form PTO-1449 filed December 19, 2001 have been considered. Applicants respectfully request correction of this understanding, if it is in error.

III. Claim Rejection Under 35 U.S.C. § 112, First Paragraph, Enablement Rejection

Claims 1-49 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. More specifically, the Office Action states, among other things, "[t]he specification does not teach how to make *any* one or more "reagents" (claims 1, 18, 20, 32, 40 and 49), *any* inhibiting reagent (claim 32), *any* antibody capable of binding to *any* lipoprotein-acute phase protein binding site (claim 36) for a method of diagnosing *any* "condition" of the patient (claim 1) or a method for testing the effectiveness of any therapeutic (claim 49)." Office Action, page 3. Applicants respectfully disagree with these assertions.

The "test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." (M.P.E.P. §2164.01, citing *In re Wands*, 858 F.2d 731, 737). Applicants respectfully submit that the specification provides substantial guidance as to how the invention may be carried out with respect to the reagents, inhibiting reagents, antibodies and conditions and methods of testing the effectiveness of therapeutics as described therein and recited in the pending claims.

Additionally, Applicants have amended claim 1 to include the recitation "wherein the one or more reagents comprises a divalent metal ion" and to recite that methods according to the present invention can be used to diagnose "hemostatic dysfunction" in a patient. Amended Claim 1 further recites that hemostatic dysfunction comprises an "inflammatory condition." Support for this amendment can be found in the specification on page 4, line 37 through page 5, line 1, among other places. Claims 18, 32, 40 and 49 have been similarly amended. The specification provides exemplary agents and/or definitions relative to these terms. More specifically, the specification notes that metal ions, specifically divalent cations, include "calcium, magnesium, manganese, iron or barium ions." Present Application, page 24, lines 30-33. The specification further provides that clot inhibitors "can be any suitable clot inhibitor such as hirudin, PPACK, heparin, antithrombin, I2581, etc." Present Application, page 25, lines 3-5. The specification states that "Haemostatic Dysfunction, as used herein, is a condition evidenced by the formation of a precipitate (prior to or in the absence of clot formation), depending upon the reagent used)." Present Application, page 11, lines 29-32. Applicants further submit that "metal ions", "clot inhibitors" and "hemostatic dysfunction" are terms that are well understood by those reasonably skilled in the art. Thus, Applicants respectfully submit that one reasonably skilled in the art would be able to make and use the invention as set forth in amended claim 1 without undue experimentation based upon the disclosure provide in the present specification, and further in view of the information known in the art.

Regarding claim 32, on page 37, lines 34-37, the specification indicates that the inhibiting reagent "inhibits at least in part, the binding of the acute phase protein to the lipoprotein." Thus, in contrast to the assertions of the Office Action on page 3, a function that is attributable to the inhibiting reagent is provided in the specification. Moreover, the specification provides exemplary inhibitors of complex formation on page 37, line 10 through page 38, line 14. These disclosures, alone or coupled with the information known in the art, would enable one reasonably skilled in the art to make and use the invention as set forth in amended claim 32 without undue experimentation.

Claim 36 has been amended to (a) correct a typographical error, (b) add "sphingomyelin", support for which can be found in the specification at page 37, lines 21-22 and (c) recite that said precipitate inhibiting reagent comprises an antibody capable of "specifically" binding to a lipoprotein-acute phase protein binding site, support for which can be found in the specification on page 38, lines 10-11 indicating that such inhibitors include antibodies to epitopes involved in complex formation. The specification further incorporates by reference *Antibodies, A Laboratory Manual*. Cold Spring Harbor Laboratory (Ed Harlow and David Lane, eds. 1988), which outlines the well-known techniques used for determining antibodies capable of specifically binding to the binding site of interest. Accordingly, these disclosures, and further in view of information known in the art, would enable one reasonably skilled in the art to make and use the invention as set forth in amended claim 36 without undue experimentation.

Claim 49 has been amended to recite that methods according to the present invention can be used to test the effectiveness of a therapeutic "for treatment of hemostatic dysfunction" and that the method comprises administering to said test subject a therapeutic "suspected of being useful in the treatment of hemostatic dysfunction." The specification provides that exemplary therapeutics "may, in general, be an antibiotic agent, an anti-inflammatory agent, an anti-coagulent agent, etc." Present Application, page 40, lines 16-18. Based upon the known pathophysiology of hemostatic dysfunction and the known pharmacological profile of various classes of compounds, Applicants respectfully submit that one reasonably skilled in the art would be able to carry out methods of testing the effectiveness of a therapeutic for treatment of a hemostatic dysfunction without undue experimentation.

Applicants note that it is only required that the specification teach one skilled in the art how to make and use the claimed invention. The issue is not whether some experimentation is necessary to optimize the invention; the relevant question is whether the amount of experimentation is "undue." In view of the claim amendments and remarks set forth above, Applicants respectfully submit that one skilled in the art relevant to the present invention would be able to practice the presently-claimed

invention without "undue" experimentation.

Accordingly, Applicants respectfully submit that claims 1, 18, 20, 32, 40 and 49 are enabled under 35 U.S.C. § 112, first paragraph, and respectfully request that the rejection of claims 1, 3-5, 7-21, 23, 25-40, 42, 43 and 45-53 be withdrawn.

IV. Claim Rejection Under 35 U.S.C. § 112, First Paragraph, Written Description Rejection

Claims 1-49 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description. In particular, the Office Action states that "[t]he specification does not reasonably provide a written description of *any* one or more "reagents" (claims 1, 18, 20, 32, 40 and 49), *any* inhibiting reagent (claim 32), *any* antibody capable of binding to *any* lipoprotein-acute phase protein binding site (claim 36) for a method of diagnosing *any* "condition" of the patient (Claim 1) or a method for testing the effectiveness of any therapeutic (claim 49)." Office Action, page 5, emphasis omitted. Applicants respectfully disagree with these assertions.

Upon review of the Final Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph, "Written Description" Requirement, 66 Fed. Reg. 1099, 1105 (Jan. 5, 2001), as suggested by the Examiner, Applicants note that these guidelines state, in part:

> The examiner has the initial burden, after a thorough reading and evaluation of the content of the application, of presenting evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support for the claims. There is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed . . .. Consequently, rejection of an original claim for lack of written description should be rare.

Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph, "Written Description" Requirement, 66 Fed. Reg. 1099, 1105 (Jan. 5, 2001).

Applicants respectfully submit that the outstanding written description rejection does not satisfy the burden set out above to conclude there is a lack of written support. Moreover, the present claims do not present one of the "rare" instances in which rejection of an originally presented claim for lack of written support is appropriate.

With respect to the claimed methods, the Office Action alleges that "[t]he specification discloses only calcium and thrombin inhibitor PPACK as reagents for the claimed method." Office Action, page 6. As noted above in Section III, the terms "metal ions" and "clot inhibitors" are described in the specification in addition to being well known in the art. As further noted above, to more particularly point out the features of the claimed invention, Applicants have amended claim 1 to include the recitation "wherein the one or more reagents comprises a metal ion."

The Office Action also alleges that "there is inadequate written description about the structure associated with function of any undisclosed "reagent" or "inhibiting reagent" without the specific amino acid or chemical structure, let alone predicting or diagnosing all conditions such as increased likelihood of mortality in patient." Office Action, page 6. The discussion set forth above regarding "reagents" applies in this particular instance as well. Concerning "inhibiting reagent", as discussed above in Section III, the specification indicates that the inhibiting reagent "inhibits at least in part, the binding of the acute phase protein to the lipoprotein." Present Application, page 37, lines 34-37. As such, a function that is attributable to the inhibiting reagent is provided in the specification. Moreover, the specification provides exemplary inhibitors of complex formation on page 37, line 10 through page 38, line 14.

With regard to an antibody capable of binding to any lipoprotein-acute phase protein binding site, the Office Action alleges that there is inadequate written description regarding the binding specificity of the antibody. *See* Office Action, page 6. As noted above in Section III, to more particularly point out the claimed invention, claim 36 has been amended to recite that the antibody "specifically" binds to a lipoprotein-acute phase protein binding site. On page 38, lines 10-11 of the present application, the specification

provides that such inhibitors include antibodies to epitopes involved in complex formation. The specification further incorporates by reference *Antibodies, A Laboratory Manual*. Cold Spring Harbor Laboratory (Ed Harlow and David Lane, eds. 1988), which outlines the well-known techniques used for determining antibodies capable of specifically binding to the binding site of interest. Thus, in contrast to the assertions of the Office Action, the specification does not provide an "infinite" number of undisclosed antibodies.

Applicants respectfully submit that it is not necessary that the present application exhaustively describe all possible reagents comprising the recited agents, inhibitory reagents and/or antibodies. "What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met." Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph, "Written Description" Requirement, 66 Fed. Reg. 1099, 1106 (Jan. 5, 2001).

In view of the disclosure provided in the specification and the amendments to the claims, Applicants respectfully submit that one skilled in the art would immediately be able to envision the reagents comprising metal ions and/or clot inhibitors, inhibitory reagents and/or antibodies as recited in the claims. Accordingly, Applicants further submit that the present claims are adequately supported by the written description set forth in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Accordingly, Applicants respectfully submit that claims 1, 3-5, 7-21, 23, 25-40, 42, 43 and 45-53 comply with the written description requirement under 35 U.S.C. § 112, first paragraph, and respectfully request that these rejections be withdrawn.

V. Claim Rejection Under 35 U.S.C. § 112, Second Paragraph, Indefiniteness Rejection

Claims 1-17, 19, 24 and 32-48 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Applicants have amended claim 1 to recite a method "of diagnosing hemostatic dysfunction." Claim 32 has been amended to recite a method "of determining the extent of inhibition of precipitation by a precipitate inhibiting reagent." Claim 18 has been amended so that claim 19 now reflects proper antecedent basis, and claim 24 has been canceled.

Accordingly, Applicants respectfully submit that claims 1-17, 19 and 32-48 are not indefinite under 35 U.S.C. § 112, second paragraph, and respectfully request that these rejections be withdrawn.

VI. Claim Rejection Under 35 U.S.C. § 102

Claims 40-43 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Rowe et al. *Clin Exp Immunol* **58**:237-244 (1984) ("Rowe et al."). Applicants respectfully disagree.

Nonetheless, Applicants have amended claim 40 to incorporate the recitations of claim 41 and claim 44, which is not subject to a rejection under 35 U.S.C. § 102(b) in view of Rowe et al. Amended claim 40 recites as follows:

> A method for diagnosis or monitoring of a hemostatic dysfunction comprising an inflammatory condition, said method comprising correlating the formation of a complex to a concentration of one or more lipoproteins comprising:
>
> a) providing a test sample from a test subject;
> b) adding one or more reagents to said test sample in order to cause formation of a complex of one or more lipoproteins and one or more acute phase proteins, wherein said reagent comprises a divalent metal cation and an acute phase protein;
> c) measuring the formation of the complex; and
> d) correlating the formation of the complex to a

> concentration of said one or more lipoproteins observed in patients with said hemostatic dysfunction, wherein the formation of an initial complex and the formation of an additional complex are measured over time so as to provide respective first and second time-dependent measurement profiles.

Applicants respectfully submit that this amendment obviates the rejection. Accordingly, Applicants respectfully submit that claims 40, 42 and 43 are not anticipated under 35 U.S.C. § 102(b) in view of Rowe et al., and respectfully request that these rejections be withdrawn.

VII. Claim Rejection Under 35 U.S.C. § 103

A. Claims 1-7, 11, 13-16 and 32-39

Claims 1-7, 11, 13-16 and 32-39 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,169,786 to Carroll (the "'786 patent") in view of Rowe et al. and Canivet et al. *Acta Anaesthesiological Belgica* **40(4)**: 263-268 (1989) ("Canivet et al."). More specifically, the Office Action states that "it would have been obvious to one of ordinary skill in the art at the time the invention was made to measure complex formation between acute phase protein such as CRP and lipoprotein such as VLDL as taught by Rowe using the assay that measured complex formation over time as taught by the '786 patent." Office Action, page 9. Applicants respectfully disagree with this assertion.

The '786 patent fails to teach or suggest the recitations of the presently claimed invention. Instead, the '786 patent teaches a method relating to Protein C. Applicants respectfully point out that Protein C is a **completely different** protein from acute phase proteins, such as C-reactive protein, as presently recited in the claims. Protein C is a regulatory protein in the clotting cascade. Acute phase proteins, such as C-reactive protein, are produced in the liver at times of tissue damage. Furthermore, the '786 patent provides an analysis based on clot formation. In the presently recited invention, a reagent is added in an amount while "causing substantially no fibrin polymerization," thus, limiting clot formation. Fibrin polymerization induces a clot to

form a precipitate. Stated differently, as reflected in the claims, the present invention involves the formation of a complex comprising an acute phase protein and at least one lipoprotein. The '786 patent involves a clot. These are two **distinguishable** precipitates. Thus, the primary reference is teaching a **different protein** and a **different precipitate**. The presently claimed invention is not directed to the clotting cascade taught by the '786 patent. These are significant differences from the recited invention.

Moreover, the '786 patent, as noted in the Office Action, **does not** teach the methods of the presently-claimed invention (Office Action, page 9). Instead, the '786 patent describes a method of determining levels of extrinsic and intrinsic clotting factors and protein C based upon the reaction rate of the observed clot formation and the first derivative of the rations rate of observed clot formation. *See* the '786 patent, abstract. The secondary references fail to teach or suggest aspects related to acute phase proteins. One of ordinary skill in the art would not consider complexes formed from acute phase proteins and lipoprotein equivalent with a blood clot, and thus, Applicants respectfully submit that there is no motivation to combine the references.

Rowe et al. describes complexes between C-reactive protein (CRP) with abnormal lipoprotein (β-VLDL). Rowe et al. indicates that the functional significance of the interaction described therein between CRP and lipoproteins is not yet known. *See* page 243. Rowe et al. speculates that the normal of role of CRP may be related in some way to lipoprotein metabolism (*see* page 243), and that CRP may contribute to pathophysiological processes, involving abnormalities of lipid deposition and distribution such as atherosclerosis and the fat embolism syndrome (*see* page 244). Rowe et al. **does not** disclose methods of diagnosing hemostatic dysfunction comprising, among other things, forming of a complex comprising at least one acute phase protein and at least one human lipoprotein, while causing substantially no fibrin polymerization, wherein the one or more reagents comprises a metal ion and/or a clot inhibitor, measuring the formation of said complex over time so as to derive a time-dependent measurement profile, and determining a slope and/or total change in the time-

dependent measurement profile so as to diagnose hemostatic dysfunction in the patient as recited in amended claim 1.

Canivet et al. merely describes that "there is a positive correlation between serum levels of HDL, cholesterol, phospholipid, ApoB and C-reactive protein after surgery, myocardial infarction, trauma and burn injury and measuring the changes in lipid profile and serum levels of CRP following surgery are of value in assessment of the host responses to critical illness." Office Action, page 9. Canivet et al. **does not** disclose methods of diagnosing hemostatic dysfunction as recited in amended claim 1.

The cited references, in combination, do not teach or suggest the presently-claimed invention as recited in claim 1. However, the Office Action states that "[i]t is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant." Office Action, page 19, citation omitted. The Office Action further states that "[t]he strongest rationale for combining references is recognition in the art that some advantage or expected beneficial result would have been produced by their combination. Office Action, pages 10-11. Applicants agree with the statements set forth in the Office Action regarding the established principles concerning combining references. Applicants respectfully disagree, however, that such motivation exists to combine the cited references for any reason.

Applicants note that the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. M.P.E.P. §2143.01, citing *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990). The Court of Appeals for the Federal Circuit has stated that, to support combining or modifying references, there must be **particular** evidence from the prior art as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed. *In re Kotzab*, 55 U.S.P.Q.2d 1313, 1317 (Fed. Cir. 2000). Applicants respectfully submit, that in this instance, one of ordinary skill in the art **would not** have been motivated to combine these particular references.

More specifically, a reference directed to clot formation, such as the '786 patent, would not be relied upon by one of ordinary skill in the art in order to arrive at the presently-claimed invention. The '786 patent **teaches away** from the presently-claimed invention which is directed to, among other things, methods that involve substantially no fibrin polymerization (i.e., no clot formation), which is in contrast to the '786 patent directed to methods relying upon clot formation. One skilled in the art would not further rely upon the remaining references in view of at least (a) the deficient teachings of Rowe et al. with respect to the present invention as recited in claim 1 as noted above, (b) the deficient teachings of Canivet et al. with respect to the present invention as recited in claim 1 as noted above, and (c) further in view of the divergent teachings of the '786 patent directed to clot formation. The divergent teachings of the '786 patent are not reconciled by either Rowe et al. or Canivet et al. absent any discussion of the measurement of relevant complexes over time. Again, Applicants concur that motivation for combining references is recognition in the art that some advantage or expected beneficial result would have been produced by their combination. However, the references must be considered in their totality and **not** in view of the teachings of the presently-claimed invention.

In this instance, the Office Action appears to pick and choose portions of the cited references to combine reference teachings excluding those teachings that are clearly deficient and/or divergent from the present invention, i.e., failure to teach measurements of relevant complexes over time and/or clot formation. When considering the reference teachings in their totality, one of ordinary skill would not be able to arrive at the present invention in view of the deficient and/or divergent teachings of the cited references as discussed in detail above.

Consequently, the cited references, even if combined, would not lead one of ordinary skill in the art to arrive at the present invention. Moreover, the allegation of the Office Action that one of ordinary skill in the art may arrive at the present invention based upon combining the cited references is clearly based upon impermissible hindsight in view of the deficient and/or divergent teachings of the

cited references. Consequently, Applicants respectfully submit that claim1 is not obvious in view of the cited references.

For at least similar reasons, Applicants respectfully submit that the cited references do not render claim 32 obvious where claim 32 is directed to methods of determining the extent of inhibition of precipitation by a precipitate inhibiting reagent. More specifically, none of the cited references are directed to determining the extent of inhibition of precipitation by a precipitate inhibiting reagent. As noted above, the '786 patent is directed to measuring clot formation and teaches away from methods directed to determining the extent of inhibition of precipitation by a precipitate inhibiting reagent. Neither Rowe et al. nor Canivet et al. cure the deficiencies associated with combining any of the cited references. Again, Applicants respectfully submit that it is **only** through impermissible hindsight combined with picking and choosing portions of the cited references to the exclusion of deficient and/or divergent teachings is one of ordinary skill in the art able to arrive at the present invention recited in claim 32.

Accordingly, Applicants respectfully submit that claims 1-5, 7, 11, 13-16 and 32-39 are not obvious under 35 U.S.C. § 103(a) in view of the cited references, and respectfully request that these rejections be withdrawn.

B. Claim 11

Claim 11 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over the '786 patent in view of Rowe et al. and Canivet et al. as applied to claims 1-7, 11, 13-16 and 32-39 and further in view of Li et al. *Biochem & Biophys Res Comm* **244**: 249-252 (1998). In particular, the Office Action states that "[i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to measure complex formation between acute phase protein such as SAP and lipoprotein such as VLDL and HDL as taught by Li et al. using the assay that measured complex formation over time as taught by the '786 patent." Office Action, page 12.

The Office Action states that "[t]he claimed invention in claim 11 differs from the combined teachings of the references only that the method wherein the acute phase protein is SAA." Office Action, page 12. As noted above, the combination of the '786 patent, Rowe et al. and Canivet et al. fail to render claim 11 obvious. Li et al. does not cure the deficiency by merely describing the binding of human serum amyloid P component (SAP) to high-density lipoprotein (HDL) or very low-density lipoprotein (VLDL), but not low-density lipoprotein (LDL). For at least the reasons presented herein, the combination of the cited references does not motivate one of ordinary skill in the art to arrive at the presently-claimed invention as recited in claim 11.

Accordingly, Applicants respectfully submit that claim 11 is not obvious under 35 U.S.C. § 103(a) in view of the cited references, and respectfully request that this rejection be withdrawn.

C. Claims 40-41 and 44-46

Claims 40-41 and 44-46 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Rowe et al. in view of the '786 patent.

As noted above in Section VI, Applicants have amended claim 40 to incorporate the recitations of claims 41 and 44. Amended claim 40 now includes recitations directed to the formation of an initial complex and the formation of an additional complex measured over time so as to provide respective first and second time-dependent measurement profiles. The Office Action acknowledges that such recitations are not taught by Rowe et al. *See* Office Action, page 13. The Office Action does state, however, that "[i]t would have been obvious to one of ordinary skill in the at the time the invention was made to measure complex formation between acute phase protein such as CRP and lipoprotein such as VLDL as taught by Rowe using the assay that measure the formation of complex (precipitation) over time as taught by the '786 patent." Office Action, page 14. Applicants respectfully disagree with this assertion.

For reasons set forth above, Applicants respectfully submit that one of ordinary skill in the art would not have been motivated to combine Rowe et al. and the '786 patent in order to arrive at the presently-claimed invention. Further, the references cannot be combined so as to arrive at the presently-claimed invention. More specifically, considering the totality of the references, the '786 patent **teaches away** from the presently-claimed invention which is directed to, among other things, methods that involve substantially no fibrin polymerization, which is in contrast to the '786 patent directed to methods relying upon clot formation. As noted previously, Rowe et al. does not reconcile the divergent teachings by merely describing complexes between CRP with abnormal lipoprotein in the absence of any discussion of the measurement of such complexes over time. Thus, for at least the reasons presented herein, the combination of the cited references does not motivate one of ordinary skill in the art to arrive at the presently-claimed invention as recited in claims 40, 45 and 46.

Accordingly, Applicants respectfully submit that claims 40, 45 and 46 are not obvious under 35 U.S.C. § 103(a) in view of the cited references, and respectfully request that these rejections be withdrawn.

VIII. New Claims 50-53 Are Patentable Over the Cited References

Applicants have added new claims 50-54. Support for new claims 50-54 can be found in the specification and claims as originally filed. Applicants respectfully submit that none of the cited references, alone or in combination, teach or suggest methods of diagnosing hemostatic dysfunction as recited in claim 50 or 54 or methods of testing the effectiveness of a therapeutic for treatment of hemostatic dysfunction as recited in claim 52.

Moreover, as noted in the Office Action, methods of diagnosing disseminated intravascular coagulation (DIC) and methods of testing the effectiveness of a therapeutic for DIC as disclosed therein are free of the prior art. *See* Office Action, pages 14-15. New claims 51 and 53 include recitations directed to this subject matter,

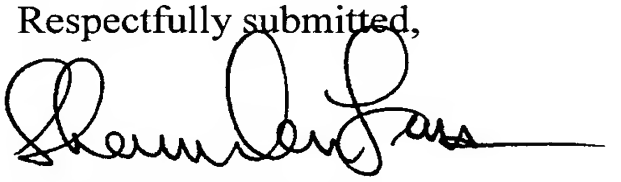
respectively. Consequently, Applicants respectfully request entry and allowance of new claims 50-54.

Conclusion

Applicants respectfully submit that, for the reasons discussed above, the claims are enabled and supported by the written description in the specification, and further the references cited in the present rejections do not disclose or suggest the present invention as claimed. Accordingly, Applicants respectfully request allowance of all the pending claims and passing this application to issue.

The Examiner is invited and encouraged to contact the undersigned directly if such contact will expedite the prosecution of the pending claims to issue. In any event, any questions that the Examiner may have should be directed to the undersigned, who may be reached at (919) 854-1400.

Respectfully submitted,



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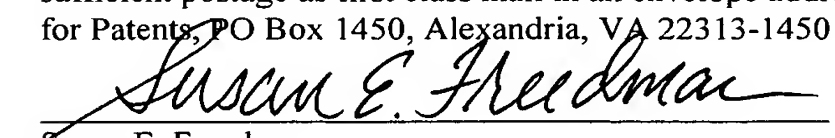

Susan E. Freedman
Date of Signature: August 25, 2004